

# Genetic basis of Parkinson's disease: inheritance, penetrance, and expression

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**Abstract:** Parkinson's disease can be caused by rare familial genetic mutations, but in most cases it is likely to result from an interaction between multiple genetic and environmental risk factors. Over recent years, many variants in a growing number of genes involved in the pathogenesis of Parkinson's disease have been identified. Mutations in several genes have been shown to cause familial parkinsonism. In this review, we discuss 12 of them (*SNCA*, *LRRK2*, *Parkin*, *PINK1*, *DJI*, *ATP13A2*, *PLA2G6*, *FBXO7*, *UCHL1*, *GIGYF2*, *HTRA2*, and *EIF4G1*). Additionally, six genes have been shown conclusively to be risk factors for sporadic Parkinson's disease, and are also discussed (*GBA*, *MAPT*, *BST1*, *PARK16*, *GAK*, and *HLA*). Many more genes and genetic loci have been suggested, but need confirmation. There is evidence that pathways involved in the rare familial forms also play a role in the sporadic form, and that the respective genes might also be risk factors for sporadic Parkinson's disease. The identification of genes involved in the development of Parkinson's disease will improve our understanding of the underlying molecular mechanisms, and will hopefully lead to new drug targets and treatment strategies.

**Keywords:** Parkinson's disease, genetics, *SNCA*, *LRRK2*, *GBA*, *MAPT*

## Introduction

Parkinson's disease is the second most common neurodegenerative disorder, after Alzheimer's disease. An estimated 1%–2% of individuals over the age of 65 years are affected, and more than 4% of the population by the age of 85 years.<sup>1</sup> Similar prevalence rates are found in different populations across the world. Because longevity is increasing in our society, these demographic age groups are growing, leading to increasing relevance of neurodegenerative diseases as a social and economic burden. Cardinal motor symptoms are tremor, rigidity, bradykinesia, and postural instability. Several nonmotor features are very common in Parkinson's disease patients, including autonomic failure, cognitive impairment, depression, olfactory deficits, psychosis, and sleep disturbance. Parkinson's disease is treated mainly with levodopa, which replaces the loss of dopamine. Complications can include the emergence of motor fluctuations and dyskinesias. Other therapeutic options include dopamine agonists, anticholinergics, monoamine oxidase inhibitors, and deep brain stimulation.<sup>2</sup> A therapy protecting against loss of neurons is not available at present.<sup>3</sup> The most frequently used diagnostic criteria are those established by the UK Parkinson's Disease Society Brain Bank,<sup>4</sup> which are based on the presence of cardinal motor features and the absence of atypical features, in addition to a positive response to levodopa treatment.<sup>2</sup> In the early course of

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the disease, it is challenging to differentiate Parkinson's disease from other parkinsonian syndromes, eg, progressive supranuclear palsy and multiple system atrophy.

During the course of the disease, dopaminergic cells are progressively lost in the substantia nigra pars compacta, resulting in a loss of dopamine in the striatal projection areas of these neurons, leading to the typical motor dysfunction, which becomes evident when approximately 80% of striatal dopamine and 50% of nigral neurons are lost.<sup>5</sup> The hallmark of the pathology of Parkinson's disease is loss of dopaminergic cells in the substantia nigra pars compacta and the presence of Lewy bodies and Lewy neurites. Lewy bodies are intracytoplasmic inclusions with a dense eosinophilic core, and are surrounded by a clearer halo on hematoxylin and eosin staining. Their principal component is the protein, alpha-synuclein, in a fibrillar form.<sup>6</sup> It is still debated whether the Lewy body is neurotoxic or reflects an attempt to protect the cell.<sup>7</sup> Lewy neurites also contain fibrillar alpha-synuclein.<sup>6</sup> They are found in nerve cell processes, in high numbers in the CA2/3 region of the hippocampus, and in the substantia nigra.<sup>8</sup> The development of neuropathological changes in Parkinson's disease is thought to occur in different stages.<sup>9</sup> The death of the dopaminergic neurons begins before the appearance of clinical symptoms and progresses throughout the course of the disease.<sup>10</sup> In the first stages, the pathology is limited to the medulla oblongata and pontine tegmentum, including the dorsal motor nucleus of the vagus nerve, the locus coeruleus, and the olfactory bulb. Motor symptoms occur later, as the substantia nigra and other nuclei within the midbrain and forebrain, eg, the nucleus basalis of Meynert, become involved. In the late stages of the disease, the pathological changes advance to the mesocortex and neocortex.<sup>9</sup>

Parkinson's disease is assumed to be multifactorial in most cases, caused by a combination of genetic and environmental risk factors. The most important "environmental" risk factor is aging. Age-dependent changes might initiate or maintain the process of neurodegeneration. In addition to that, a few toxic exposures (eg, MPTP, and certain pesticides) have been identified as selectively damaging dopaminergic neurons, but their relationship to sporadic Parkinson's disease is still unclear. A few protective factors (caffeine, nicotine, and possibly nonsteroidal anti-inflammatory agents) have also been identified by epidemiologic studies.<sup>11</sup> A family history is reported by approximately 10%–20% of patients.<sup>12</sup> Genetic involvement has been substantiated in recent decades by the finding of several disease-causing genes and risk factors.

Genes causing monogenic forms of the disease are usually identified by linkage studies. This approach examines families with multiple affected and unaffected relatives, defining a rare genetic variant (pathogenic mutation) that is segregating with the disease. Genes that represent risk factors are mostly identified by association studies. Genetic risk variants are generally much more common in a population than high-penetrance disease-causing mutations, and if the frequency is higher in cases than in controls, this indicates that the variant confers a risk for a given disease. Because the effect strength of these genetic risk variants is usually low, association analyses need to include large cohorts of patients and controls. An unbiased approach for association analyses are genome-wide association studies. Linkage analyses have resulted in identification of several loci (*PARK1-PARK13*, *PARK15*, and *EIF4G1*). Association analyses have identified several risk factors (*SNCA*, *LRRK2*, *GBA*, *MAPT*, *BST1*, *PARK16*, *GAK*, and *HLA*).

Interestingly, the Parkinson's disease-causing genes seem to fall into several classes. The dominant forms cause a phenotype closely resembling sporadic Parkinson's disease. Some of the recessive forms present with an earlier age at onset and as pure parkinsonism, while others cause parkinsonism with additional clinical features (*ATP13A2*, *PLA2G6*, and *FBXO7*). In this paper we discuss the most important genes relevant to Parkinson's disease (listed in Table 1) and their associated clinical features.

## Autosomal dominant Parkinson's disease genes

### *SNCA* (*PARK1/PARK4*)

*SNCA* was the first causal Parkinson's disease gene ever identified. Its mutations cause autosomal dominant Parkinson's disease. The gene encodes the protein alpha-synuclein, which has been detected as the main component of Lewy bodies and Lewy neurites.<sup>6</sup> The function of alpha-synuclein is still unknown. It binds to synaptic vesicles<sup>13</sup> and may be involved in brain plasticity.<sup>14</sup> The protein is expressed widely in the brain and localizes mostly to presynaptic nerve terminals.<sup>15</sup> Natively unfolded, alpha-synuclein can oligomerize and form fibrils.<sup>16</sup> These fibrillar moieties are the components of Lewy bodies in both familial and sporadic PD.<sup>6</sup> It is controversial if these fibrils are toxic or protective to the cell. The discovery of the linkage of autosomal dominant Parkinson's disease to chromosome 4q21<sup>17</sup> was followed by identification of a pathogenic missense mutation in *SNCA*.<sup>18</sup> To date, three missense mutations (A53T,<sup>18</sup> A30P,<sup>19</sup> and E46K<sup>20</sup>), duplications,<sup>21,22</sup>

**Table 1** Summary of genes and loci underlying Parkinson's disease

Locus	Gene	Chromosomal location	Inheritance	Type of parkinsonism
PARK1/PARK4	SNCA	4q21	AD + risk	LOPD/EOPD, dementia
PARK2	<i>Parkin</i>	6q25-q27	AR	EOPD
PARK3	Unknown	2p13	AD	LOPD
PARK5	UCHL1	4p14	AD	LOPD
PARK6	<i>PINK1</i>	1p36	AR	EOPD
PARK7	<i>DJI</i>	1p36	AR	EOPD
PARK8	<i>LRRK2</i>	12q12	AD + risk	LOPD
PARK9	<i>ATP13 A2</i>	1p36	AR	EOPD, Kufor-Rakeb syndrome
PARK10	Unknown	1p32	Unknown	LOPD
PARK11	GIGYF2	2q37	AD	LOPD
PARK12	Unknown	Xq21-25	X-linked	LOPD
PARK13	HTRA2	2p12	AD	LOPD
PARK14	<i>PLA2G6</i>	22q13	AR	EOPD, dystonia-parkinsonism
PARK15	<i>FBXO7</i>	22q12-q13	AR	EOPD, pallido-pyramidal syndrome
PARK16	Unknown	1q32	Risk	LOPD
PARK17	GAK	4p16	Risk	LOPD
PARK18	<i>HLA</i>	6p21	Risk	LOPD
–	<i>EIF4G1</i>	3q27	AD	LOPD
–	<i>GBA</i>	1q21	Risk	LOPD
–	<i>MAPT</i>	17q21	Risk	LOPD
–	<i>BST1</i>	4p15	Risk	LOPD

**Abbreviations:** AD, autosomal dominant; AR, autosomal recessive; EOPD, early-onset Parkinson's disease; LOPD, late-onset Parkinson's disease.

and triplications<sup>23</sup> of the entire gene have been identified. Duplications of the gene lead to a 1.5-fold increase of the protein, whereas triplications lead to a two-fold increase.<sup>24</sup> These findings suggest that already the increased concentrations of wild-type alpha-synuclein protein appear to be toxic to neurons. A point mutation in alpha-synuclein might lead to an increased tendency to form aggregates,<sup>25</sup> pointing to a gain-of-function hypothesis. Another hypothesis suggests that mutated *SNCA* leads to a compensatory overexpression of the wild-type allele. *SNCA* mutations are rare, accounting for less than 1% in Caucasian cases of Parkinson's disease.<sup>26,27</sup> Mutations have been identified in Caucasian and Asian families, and in some patients with apparently sporadic Parkinson's disease.<sup>27,28</sup> Some of the multiplications appear to have different genomic sizes in different families, suggesting that the mutations arose independently.<sup>29</sup> The penetrance of duplication carriers is estimated to be around 40%.<sup>28,30</sup> Accordingly, there are also reports of asymptomatic carriers.<sup>27,28,30,31</sup> The clinical phenotype presents as levodopa-responsive Parkinson's disease, with relatively early age at onset, rapid progression,<sup>32</sup> a higher prevalence of dementia, and psychiatric and autonomic disturbances.<sup>27,33</sup> Some patients show atypical clinical features, including myoclonus or multiple system atrophy.<sup>33</sup> There is some evidence of genotype-phenotype correlation. Patients with *SNCA* duplications mostly show a typical late-onset Parkinson's disease phenotype with slow

progression and no atypical features. Patients with a *SNCA* triplication or the A53T missense mutation have an earlier age at onset (around 34 years), and carriers of a triplication, the A53T or the E46K missense mutation, present more frequently with dementia than duplication carriers or carriers of the A30P missense mutation.<sup>20–23,28,31,33,34</sup> Pathological studies describe *SNCA* mutation carriers with typical brain stem<sup>32</sup> or diffuse Lewy body disease.<sup>20,24</sup> Common variants in *SNCA* have been found to be a risk factor in sporadic Parkinson's disease. One signal represented by a dinucleotide repeat polymorphism (NACP-Rep1) is located in the promoter region;<sup>35</sup> another signal maps to the 3' end of the gene.<sup>36</sup> *SNCA* was identified as a risk factor in all genome-wide association studies conducted so far.<sup>37–43</sup> The variants associated with increased risk of Parkinson's disease might lead to a slightly higher expression of alpha-synuclein.<sup>44</sup>

### *LRRK2* (PARK8)

Mutations in *LRRK2* cause autosomal dominant Parkinson's disease. The function of the encoded protein is unknown. It has been suggested to play a role in intracellular signaling pathways. The protein contains a kinase, a GTPase, and several protein–protein interaction domains.<sup>45</sup> *LRRK2* is expressed widely in the brain, and also in other organs.<sup>45,46</sup> It is localized to membranes and vesicles, such as mitochondria, lysosomes, and endosomes.<sup>47</sup> The locus was linked to chromosome 12q12,<sup>48</sup> and subsequently several missense

mutations were identified in the *LRRK2* gene.<sup>45,46</sup> Since then, many missense mutations have been identified in *LRRK2*, but the pathogenicity is only clearly established for six of them (ie, R1441C, R1441G, R1441H, Y1699C, G2019S, and I2020T).<sup>49</sup> The mechanism by which *LRRK2* mutations contribute to the development of Parkinson's disease might be an increase in kinase activity,<sup>50</sup> an impairment of the GTPase function,<sup>51</sup> or an alteration in ability to dimerize,<sup>52</sup> depending on which domain the mutation occurs in. Mutations in *LRRK2* are the most common cause of familial Parkinson's disease. The frequency in familial cases is 5%–15%, and in sporadic cases is around 1% in patients with Caucasian ancestry.<sup>53–55</sup> One mutation, G2019S, is particular common, occurring in up to 2%–7% of Caucasian cases of familial Parkinson's disease<sup>49,54,56,57</sup> and in 1% of sporadic cases.<sup>49</sup> In some populations, the frequency of G2019S is surprisingly high, being up to 20% in Ashkenazi Jews<sup>58</sup> and 40% in North African Arabs.<sup>59</sup> Occurrence of *LRRK2* mutations in apparently sporadic patients and in healthy control individuals<sup>49,56</sup> suggests a reduced penetrance. Estimations of the penetrance for G2019S range from 32% to 74%, depending on the familial background of the families analyzed.<sup>49,55,60</sup> G2019S was also found in homozygosity, but with no difference in clinical phenotype compared with heterozygous carriers.<sup>57</sup> This mutation is observed in a limited number of haplotypes, indicating that there are only a few founders.<sup>56,61</sup> Similarly, the R1441G mutation was transmitted from a common founder in the Basque population,<sup>61</sup> whereas the R1441C has several different founder haplotypes.<sup>54</sup> Some mutations occur only in the Asian population, where the G2019S seems to be rare or absent.<sup>49,62</sup> The clinical phenotype strongly resembles typical late-onset Parkinson's disease, with an average age at onset of 59 years.<sup>45,53</sup> Single cases cannot be distinguished from sporadic idiopathic Parkinson's disease. On average, they seem to have a slightly more benign course of disease, slower progression, and lower frequency of dementia and psychiatric complications.<sup>49,53</sup> One study reported that the predominant sign in *LRRK2*-related Parkinson's disease is tremor.<sup>49</sup> Pathological signs in *LRRK2* mutation carriers are typical alpha-synuclein Lewy bodies in most cases, but some cases show atypical pathology, like diffuse Lewy body disease, tau pathology, neuronal loss without intracellular inclusions, and motor neuron disease.<sup>45,63</sup> These different pathological changes can even be found among members of the same family, with the same pathogenic mutation.<sup>45</sup> Two *LRRK2* variants, ie, G2385R and R1628P, were identified as risk factors in the Asian population.<sup>64,65</sup> These variants are very rare or absent in other populations. In a Caucasian and

an Asian genome-wide association study, variation 5' of the gene was identified as a risk factor in sporadic Parkinson's disease.<sup>38,39</sup>

## Autosomal recessive Parkinson's disease genes

### *Parkin* (*PARK2*)

Mutations in *PARK2* (*Parkin*) cause autosomal recessive Parkinson's disease. *Parkin*, the encoded protein, belongs to the ubiquitin E3 ligases.<sup>66</sup> It interacts with ubiquitin-conjugating enzymes (E2s) to catalyze the attachment of ubiquitin to protein targets, thus tagging these proteins for destruction by the proteasome.<sup>66</sup> Additionally, *Parkin* is involved in mitochondrial maintenance<sup>67,68</sup> and might induce autophagy of dysfunctional mitochondria.<sup>69</sup> *Parkin* is expressed in many tissues, including various brain regions and the substantia nigra.<sup>70</sup> It is predominantly localized in the cytosol, but is also present in vesicles, the Golgi complex, the endoplasmic reticulum, and the outer mitochondrial membrane.<sup>71</sup> The locus was first linked to chromosome 6q26,<sup>72</sup> followed by the detection of mutations in the gene *Parkin*.<sup>70</sup> Many mutations have been reported since then, including missense, nonsense, indels, exonic deletions, duplications, and triplications.<sup>73,74</sup> Most of the exonic rearrangements have likely occurred as relatively recent new mutational events. Point mutations, on the other hand, are mostly transmitted from common founders.<sup>75</sup> These mutations are involved in development of Parkinson's disease probably by a loss-of-function mechanism.<sup>66</sup> Patients with Parkinson's disease and *Parkin* mutations have a mean age at onset of 32 years in the Caucasian population.<sup>74</sup> Hence, *Parkin* mutations are the most common cause of early-onset Parkinson's disease, occurring in up to 50% of those with age at onset under 25 years (and only 3%–7% in those with age at onset 30–45 years).<sup>73,74</sup> However, cases with very early onset (<30 years) represent probably only 1%–2% of cases overall. Mutations were identified in familial as well as in sporadic patients and in populations of all ethnic origins. The penetrance for homozygous or compound heterozygous mutation carriers seems to be 100%. Patients with *Parkin* mutations present with levodopa-responsive Parkinson's disease accompanied frequently by motor fluctuations and dyskinesias that often develop early in the course of treatment.<sup>74,76</sup> A high percentage of patients show dystonia, usually in a lower extremity at the onset of disease.<sup>74</sup> Additionally, psychiatric abnormalities can arise.<sup>76</sup> The disease progression is slow. Missense mutations might lead to faster progression of the disease and a higher Unified Parkinson's Disease Rating Scale motor score than truncating mutations. Missense mutations

in functional domains of the gene can result in an earlier age at onset.<sup>77</sup> Patients carrying mutations in *Parkin* rarely show the presence of Lewy bodies, although nigrostriatal cell loss is usually severe.<sup>78,79</sup> Heterozygous mutations in *Parkin* may be a risk factor for Parkinson's disease. However, several studies have reported controversial results.<sup>80,81</sup> Further large-scale studies will be needed to elucidate the risk in heterozygous carriers.

### ***PINK1 (PARK6)***

Mutations in *PINK1* also cause autosomal recessive Parkinson's disease. The protein encoded by *PINK1* is located in the mitochondrial membranes and expressed ubiquitously, including the brain.<sup>82</sup> It is involved in the mitochondrial response to cellular and oxidative stress.<sup>83</sup> By interaction with parkin, *PINK1* might protect neurons against mitochondrial dysfunction and proteasome-induced apoptosis.<sup>84</sup> The locus was first linked to chromosome 1p36,<sup>85</sup> and then causal missense and nonsense mutations in the gene *PINK1* were detected.<sup>83</sup> Several missense, nonsense, frameshift mutations, and large deletions of multiple exons were identified thereafter.<sup>86–91</sup> The mutations seem to impair the function of the protein.<sup>83</sup> Mutations in *PINK1* are a rare cause of early-onset Parkinson's disease, accounting only for 2%–4% of early-onset cases in Caucasian populations<sup>86,91</sup> and 4%–9% in Asian populations.<sup>87,90</sup> The penetrance for homozygous and compound heterozygous mutation carriers seems to be 100%. The clinical phenotype is similar to that caused by mutations in *Parkin*.<sup>90</sup> The early onset (24–47 years) is accompanied by slow disease progression and a good response to levodopa.<sup>86,87</sup> Sometimes dementia occurs. Some patients show additional psychiatric disturbances, particularly anxiety and depression, which is only relatively rarely observed in *Parkin*-related cases.<sup>92</sup> Occasionally, *PINK1* mutations are found in late-onset Parkinson's disease, restless legs syndrome with parkinsonism, and dopa-responsive dystonia.<sup>87–89</sup> Pathological changes in a single reported case were those of typical Lewy body disease.<sup>93</sup>

### ***DJ1 (PARK7)***

Mutations in *DJ1* are another, but very rare, cause of autosomal recessive Parkinson's disease. The protein DJ1 is a sensor for oxidative stress and may mediate neuroprotection.<sup>94</sup> It is translocated to the mitochondrial membrane upon presence of oxidative stress, and appears to act as an antioxidant.<sup>94</sup> Nigral dopamine neurons are highly exposed to oxidative stress, highlighting the function of DJ1 as being particularly interesting in the pathogenesis of Parkinson's disease. DJ1 is

expressed in most tissues, including the brain, and has been found in neuronal and glial cells.<sup>95</sup> The gene was originally mapped to chromosome 1p36.<sup>96</sup> After the first discovery of a missense mutation and an exonic deletion,<sup>97</sup> a few other missense and splice-site mutations, as well as deletions, were identified in homozygous or compound heterozygous states.<sup>98,99</sup> One mutation, the *L166P*, leads to a less stable protein<sup>100</sup> and to the reduction of antioxidative activity,<sup>101</sup> implicating a loss-of-function mechanism for *DJ1* mutations in general. Mutations in *DJ1* seem to be very rare, accounting for only 1% of early-onset cases,<sup>98,99</sup> but the penetrance for homozygous and compound heterozygous mutation carriers seems to be 100%. Similar to the other recessive Parkinson's disease forms, the clinical picture includes an early onset (20–40 years), good response to levodopa, and slow progression. In one family, Parkinson's disease was accompanied by dementia and amyotrophic lateral sclerosis.<sup>102</sup> Some patients with *DJ1* show psychiatric symptoms,<sup>103</sup> short stature, and brachydactyly,<sup>104</sup> suggesting that the phenotype can vary.

### **Autosomal recessive genes causing parkinsonism with atypical features** ***ATP13A2 (PARK9)***

Mutations in *ATP13A2* cause autosomal recessive parkinsonism with a complex phenotype. *ATP13A2* encodes a lysosomal membrane protein with an ATPase domain, predominantly expressed in the brain.<sup>105</sup> The exact function of this protein is still unknown. The locus was linked to chromosome 1p36, and the gene was subsequently identified as *ATP13A2*.<sup>105</sup> Since then, several missense mutations, as well as splice-site and small deletions and insertions were identified.<sup>106,107</sup> Some evidence indicates that the mutated protein is unstable and degraded.<sup>105</sup> Mutation analyses in Caucasians show that these mutations are only a very rare cause of parkinsonism.<sup>108</sup> The phenotype is atypical parkinsonism, also described as Kufor-Rakeb syndrome. Patients with mutations in *ATP13A2* have a very early onset (11–16 years)<sup>109,110</sup> and a rapid progression of parkinsonian symptoms. They are levodopa-responsive, have pyramidal signs, and show spasticity and supranuclear gaze palsy.<sup>109,110</sup> Additionally, some also show facial, faucal, and finger minimyoclonus, visual hallucinations, and dystonic oculogyric spasm.<sup>110</sup> A few cases have been reported with more typical early-onset Parkinson's disease.

### ***PLA2G6 (PARK14)***

Mutations in *PLA2G6* have been identified in autosomal recessive families. *PLA2G6* encodes a calcium-independent



phospholipase A2 enzyme that catalyzes hydrolysis of glycerophospholipids and is critical in cell membrane homeostasis.<sup>111</sup> Two childhood-onset disorders are caused by mutations in *PLA2G6*, ie, infantile neuroaxonal dystrophy and neurodegeneration with brain iron accumulation or Karak syndrome.<sup>111</sup> The pathology includes axonal swellings and spheroid bodies, and some show alpha-synuclein-positive Lewy bodies. The clinical phenotype is characterized by a young-onset progressive extrapyramidal–pyramidal syndrome with visual disturbances, early cerebellar signs, and a late-onset parkinsonian syndrome. By homozygosity mapping, missense mutations were identified in families with adult-onset levodopa-responsive dystonia-parkinsonism.<sup>112</sup> Thereafter, several other mutations were identified in additional families, but the frequency in Parkinson's disease seems to be very low.<sup>113</sup> Parkinson's disease patients with *PLA2G6* mutations also show pyramidal signs, cognitive dysfunction, and levodopa-induced dyskinesias, but no cerebellar signs.<sup>112,114</sup> Dystonia is not present in all patients, as well as iron accumulation in the brain.<sup>112,114</sup>

### ***FBXO7 (PARK15)***

Mutations in *FBXO7* have been found in autosomal recessive families. The protein encoded by *FBXO7* might serve as a molecular scaffold in the formation of protein complexes. It is also suggested to play a role in the ubiquitin-proteasome protein degradation pathway.<sup>115</sup> The locus was originally linked to chromosome 22q1 in a family with juvenile Parkinson pyramidal syndrome. Subsequently, a missense mutation was identified in the *FBXO7* gene.<sup>115</sup> Additional cases with missense and splice site mutations were thereafter identified.<sup>116</sup> The frequency of mutations in this gene seems to be very low.<sup>117</sup> Patients with mutations in *FBXO7* have early-onset, progressive parkinsonism and pyramidal tract signs, described as the pallido-pyramidal syndrome. Dystonia can be present in childhood, whereas pyramidal signs of the lower limbs can occur in later stages of the disease.<sup>116</sup>

## **Autosomal dominant genes and loci with unclear pathogenicity**

### ***UCHL1 (PARK5)***

Mutations in *UCHL1* have been suggested to cause autosomal dominant Parkinson's disease. The encoded protein, UCHL1, is a component of the ubiquitin-proteasome system, removing abnormal and misfolded proteins, and generating free ubiquitin monomers.<sup>118</sup> It is highly and specifically expressed in neurons,<sup>119</sup> and is one of the most abundant proteins in the brain.<sup>118</sup> It seems to be localized to synaptic vesicles.

*UCHL1* was sequenced in a candidate gene approach and one family was found to harbor a missense mutation (I93M).<sup>120</sup> To date, no other pathogenic mutations of this gene have been identified. The I93M mutation leads to a 50% loss of catalytic hydrolase activity, suggesting a loss-of-function mechanism.<sup>120,121</sup> Another hypothesis assumes a gain-of-function through alteration of the protein structure.<sup>121</sup> There was an unaffected carrier in the affected family, suggesting reduced penetrance.<sup>120</sup> This *UCHL1* family presented with typical Parkinson's disease, a good response to levodopa, and an age at onset of 49–51 years.<sup>120</sup> There are no pathology data available. Later, a common missense variant (S18Y) was identified as being associated with risk of Parkinson's disease.<sup>122</sup> This S18Y mutation is thought to have a protective effect by decreasing ligase activity<sup>123</sup> and increasing hydrolase activity.<sup>121</sup> However, studies trying to replicate the association have yielded conflicting results.<sup>124–126</sup> Because there was only one family with a potentially pathogenic mutation that was not fully segregating and no further evidence for *UCHL1* as a genetic risk factor, its role in Parkinson's disease has become very questionable.

### ***GIGYF2 (PARK11)***

The *PARK11* locus was mapped by linkage to chromosome 2q37 with a dominant model in families with Parkinson's disease.<sup>127</sup> Later, mutations in the *GIGYF2* gene were found to segregate with typical Parkinson's disease in several small families.<sup>128</sup> *GIGYF2* encodes a component of the insulin-signaling pathway and is expressed in the brain.<sup>129</sup> However, replication studies have failed to demonstrate the pathogenicity of these mutations,<sup>130,131</sup> and the original *PARK11* family used to define the locus has no mutation in *GIGYF2*.<sup>132</sup> Therefore, it seems unlikely that *GIGYF2* plays a role in susceptibility to Parkinson's disease. In contrast with linkage approaches in single large families, the analysis of several families together is challenged by the heterogeneity of Parkinson's disease. The fact that only small families were used in the *GIGYF2*-linkage might have additionally biased the analysis.

### ***HTRA2 (PARK13)***

Mutations in the *HTRA2* gene were found in a small autosomal dominant family by a candidate gene approach.<sup>133</sup> *HTRA2* encodes for a serine protease that transfers from the mitochondria to the cytosol upon stimulation.<sup>134</sup> One missense mutation (G399S) was found to segregate in a family with Parkinson's disease. Another missense mutation (A141S) was more frequently detected in cases than

in controls, indicating a risk factor. This A141S mutation leads to a decrease in protease function, suggesting a loss-of-function mechanism.<sup>133</sup> But again, replication studies failed to demonstrate pathogenicity of the G399S mutation, which was also found in controls,<sup>135</sup> and could not detect an association of A141S with risk for Parkinson's disease.<sup>136</sup>

### **EIF4G1**

A mutation in the gene *EIF4G1* was found to be segregating with late-onset Parkinson's disease in an autosomal dominant family.<sup>137</sup> The encoded protein, EIF4G1, is a translation initiation factor and might be involved in stress response. Loss of EIF4G1 leads to impaired nutrient sensing and mitochondrial bioenergetics, while promoting autophagy. The same mutation was thereafter identified in several Caucasian families, but not in control individuals. These findings still need to be replicated.

### **PARK3, PARK10, PARK12**

Several other loci have been mapped in families with Parkinson's disease, but the genes have not yet been identified. *PARK3*, *PARK10*, and *PARK12* were found by linkage analyses in families with typical late-onset Parkinson's disease.<sup>127,138,139</sup> The *PARK3* locus includes the *SPR* gene. Polymorphisms in this gene have been found to be associated with age at onset in patients with Parkinson's disease.<sup>140</sup> Its protein is involved in the dopamine synthesis pathway. Future studies will be necessary to elucidate definitively the role of these loci in the pathogenesis of Parkinson's disease.

## **Genetic risk factors**

### **GBA**

Homozygous or compound heterozygous mutations in the *GBA* gene cause Gaucher disease, and single heterozygous mutations have recently been found to be an important risk factor for Parkinson's disease. Gaucher disease is a rare, recessively inherited, lipid storage disorder with multisystemic manifestation, including involvement of the liver, spleen, bone marrow, lungs, and nervous system.<sup>141</sup> Some patients with Gaucher disease develop parkinsonism.<sup>142</sup> The disease is characterized by accumulation of the glycolipid, glucosylceramide, in the lysosomal compartment of various cells. Relatives of patients with Gaucher disease have a higher prevalence of Parkinson's disease,<sup>143</sup> which led to the discovery that heterozygous carriers of mutations in *GBA* are at increased risk of Parkinson's disease.<sup>144</sup> The association of *GBA* mutations with Parkinson's disease has been confirmed in a large meta-analysis involving many

populations worldwide.<sup>145</sup> *GBA* encodes glucosylceramidase, a lysosomal enzyme, which cleaves glucosylceramide to ceramide and glucose. Over 300 mutations causing Gaucher disease have been found in *GBA*, and are considered to be loss-of-function mutations. The mutations in Gaucher disease lead to accumulation of the substrate in the lysosome, but how heterozygous mutations contribute to the pathogenesis of Parkinson's disease is still unclear. Because alpha-synuclein is at least in part degraded by the lysosome, decreased activity of GBA could lead to incomplete degradation and subsequent aggregation of alpha-synuclein. Likewise, misfolded GBA could impair lysosomal function and the autophagy pathway in general.<sup>146</sup> Another hypothesis is based on the observation that alpha-synuclein binds to lipids in the plasma membrane<sup>147</sup> and this binding influences the fibrillization capacity of alpha-synuclein. Actually, it has been shown that alpha-synuclein binds to glycosphingolipids containing glucosylceramide. Decreased activity of mutated GBA leads to accumulation of glucosylceramide, and might therefore influence lipid metabolism and aggregation of alpha-synuclein.<sup>146</sup> The frequency of *GBA* mutations among Caucasian patients with Parkinson's disease has been found to be 7%, as compared with 1% in control individuals. The frequency is much higher in Ashkenazi Jews, with 20% of Parkinson's disease patients being carriers versus 4% in controls.<sup>145,148</sup> In Caucasians, the two most common mutations are N370S and L444P, accounting for approximately 50% of all identified mutation carriers.<sup>145,148</sup> In Asians, the L444P mutation is the most common mutation, and the N370S is only rarely found.<sup>149</sup> In Ashkenazi Jews, the N370S is the most common mutation.<sup>145</sup> The clinical phenotype resembles typical late-onset sporadic Parkinson's disease with alpha-synuclein-positive Lewy body pathology and a higher frequency of diffuse neocortical Lewy body pathology.<sup>150</sup> The onset is reported to be somewhat earlier, especially in carriers of the more severe mutations, eg, L444P.<sup>148</sup> Parkinson's disease patients with the *GBA* mutation often have more severe nonmotor symptoms, including cognitive changes.<sup>145</sup> Bradykinesia as the onset symptom and levodopa-induced dyskinesias also seem to be more frequent.<sup>148</sup> *GBA* mutations are also considered to be a risk factor for dementia with Lewy bodies.<sup>151</sup>

### **MAPT**

*MAPT* is a known risk factor for progressive supranuclear palsy and corticobasal degeneration, and mutations have been found to cause one form of familial frontotemporal dementia.<sup>152–154</sup> Many studies, including all published genome-wide association studies in Caucasian populations,

have confirmed the *MAPT* locus as a risk factor for Parkinson's disease.<sup>37–43,155,156</sup> *MAPT* encodes the microtubule-associated protein tau, which plays a key role in the organization and integrity of the cytoskeleton.<sup>157</sup> It is primarily expressed in neurons. Tau inclusions are found in several neurodegenerative diseases, referred to as “tauopathies”, including progressive supranuclear palsy, corticobasal degeneration, frontotemporal dementia, and Alzheimer's disease. On the other hand, Parkinson's disease, multiple system atrophy, and dementia with Lewy bodies, are referred to as “synucleinopathies”, due to the accumulation of alpha-synuclein. An interplay between the two pathophysiological mechanisms underlying these diseases has been repeatedly suggested.<sup>158</sup> The *MAPT* locus is the longest region of linkage disequilibrium in Caucasians.<sup>159</sup> There are two forms of this genomic region in Caucasians, ie, the H1/H2 haplotypes. The different haplotypes originate from a 900 kb inversion,<sup>160</sup> which might have been introduced by the Neanderthals into the Caucasian genome.<sup>161</sup> Because the H1 haplotype is associated with risk of Parkinson's disease and other neurodegenerative disorders, the H2 haplotype might have been under positive selection since that time. This inversion is absent in the Asian population, which is why an Asian genome-wide association study did not identify *MAPT* as a risk factor. The H1 haplotype can be subdivided into subhaplotypes.<sup>162</sup> Which of these subhaplotypes in particular is associated with Parkinson's disease remains to be elucidated, but it seems that the risk variant increases expression of tau.

### ***BST1***

*BST1* was identified as a risk factor in sporadic late-onset Parkinson's disease in an Asian genome-wide association study.<sup>39</sup> The encoded protein catalyzes formation of cyclic ADP-ribose and might play a role in Ca<sup>2+</sup> homeostasis.<sup>163</sup> The association with Parkinson's disease was replicated in two Caucasian genome-wide association studies,<sup>42,43</sup> but could not be replicated in one Caucasian<sup>38</sup> and one Asian study.<sup>164</sup> Allele frequencies differed markedly between the studies, and effect sizes seem to be lower in Caucasians. Further studies will be necessary to clarify the role of *BST1* in Parkinson's disease.

### ***PARK16***

A locus on chromosome 1q32 was identified to be associated with Parkinson's disease in an Asian genome-wide association study.<sup>39</sup> This region, designated *PARK16*, contains five genes. The locus was replicated in two Caucasian genome-wide association studies and several association

studies.<sup>38,43,164</sup> Potential disease-causing mutations were subsequently reported in families with typical Parkinson's disease for two of the genes in this locus, ie, *RAB7L1* and *SLC41A1*.<sup>165</sup> The role of the *PARK16* locus in monogenic families and as a risk factor needs to be determined further in future studies.

### ***GAK (PARK17)***

In a Caucasian genome-wide association study involving familial cases of Parkinson's disease, a locus on chromosome 4p16 was identified.<sup>37</sup> This locus was replicated in several other association studies as being significantly associated with Parkinson's disease.<sup>41,43,156</sup> *GAK* is one of the coding genes in this region. It encodes for a cell cycle regulator that is ubiquitously expressed.<sup>166</sup> This protein might also be involved in clathrin-mediated endocytosis, like vesicle trafficking,<sup>167</sup> which might be a link to alpha-synuclein. *GAK* is differentially expressed between Parkinson's disease cases and controls in the substantia nigra.<sup>168</sup>

### ***HLA (PARK18)***

*PARK18* was identified as a risk factor in a recent genome-wide association study.<sup>41</sup> The locus contains the *HLA* region. *HLA* DRA and DRB proteins form the Class II *HLA-DR* antigens, which are expressed by antigen-presenting cells, including microglia in the brain. The genetic region is highly variable. Variation in the *HLA-DR* genes as a risk factor for Parkinson's disease fits with the observations from previous studies implicating chronic inflammation and humoral immunity in the pathogenesis of Parkinson's disease.<sup>169,170</sup>

## **Summary**

Two genes (*SNCA* and *LRRK2*) have been conclusively linked to autosomal dominant Parkinson's disease. These two genes also represent risk factors in the sporadic form of the disease. Three genes (*Parkin*, *PINK1*, and *DJ1*) have been shown to cause pure autosomal recessive Parkinson's disease with early age at onset. Autosomal recessive parkinsonism in a complicated form is caused by mutations in three genes (*ATP13A2*, *PLA2G*, and *FBXO7*). There are more genes and loci suggested to be involved in monogenic Parkinson's disease, but require replication before firm conclusions could be drawn (*UCHL1*, *GIGYF2*, *HTRA2*, *EIF4G1*, *PARK3*, *PARK10*, and *PARK12*). Six additional genes have been discussed as risk factors in sporadic Parkinson's disease (*GBA*, *MAPT*, *BST1*, *PARK16*, *GAK*, and *HLA*). Many more variants have been found to be associated with



Parkinson's disease, most of which need further replication in independent studies.

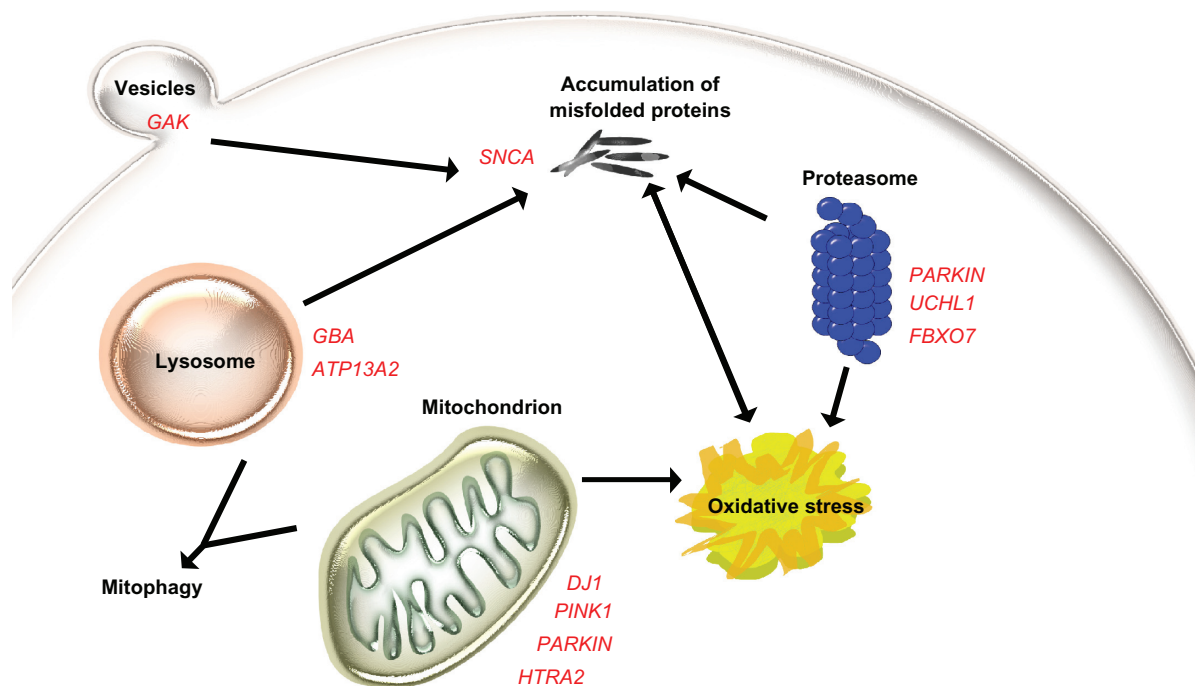
Mendelian forms of Parkinson's disease account for less than 10% of all Parkinson's disease cases in most populations. The Ashkenazi Jewish population is an exception, because *LRRK2* and *GBA* mutations are found at a higher frequency. Since the discovery that *SNCA* and *LRRK2* not only cause the monogenic form of Parkinson's disease, but also act as risk factors in the sporadic form, it has been suggested that different alterations in the same gene can be important in both forms. Other familial genes will be tested for association with risk and, in turn, known risk genes will be tested for causing the familial form of the disease.

The discovery of causal mutations in Parkinson's disease has given researchers the opportunity to identify young presymptomatic mutation carriers who can be followed longitudinally to identify premotor changes using clinical, biochemical, and imaging methods. These biomarkers can be used to investigate the early phases of the disease in a general way, hopefully leading to earlier diagnoses and neuroprotective treatment strategies.

Many more susceptibility loci will likely be uncovered in the near future. A recent meta-analysis of five Caucasian genome-wide association studies revealed many additional

risk genes.<sup>171</sup> Future research methods will not only include traditional linkage analysis and genome-wide association studies, but also new methods, like meta-analysis of genome-wide association studies, gene-gene and gene-environment interaction studies, pathway analysis, and copy number variant analysis, as well as whole exome sequencing. It may also be promising to examine different and as yet unstudied populations. The identification of new genes involved in the pathogenesis of Parkinson's disease is challenging because it has a late-in-life onset, which decreases the availability of large familial pedigrees. Furthermore, the underlying genetics are complex, including mutations with reduced penetrance and interaction of several risk factors. Replication studies have to consider that distinct populations differ in the composition of their risk factors, making comparisons across populations difficult.

The genes identified so far are involved in pathways that might be of general interest in the development of Parkinson's disease, in particular, those involving the mitochondria, like mitochondrial dysfunction, oxidative stress, mitochondrial fission and fusion, and mitophagy. Another broad field includes pathways involved in aberrant protein degradation, and proteasomal and lysosomal dysfunction (Figure 1). Although our knowledge about the pathogenesis



**Figure 1** Model of the pathogenesis of Parkinson's disease. The central step in Parkinson's disease pathogenesis is proposed to be the accumulation of alpha-synuclein, while the regular function of alpha-synuclein (*SNCA*) might involve the formation of vesicles, like GAK. Mitochondrial maintenance and response to oxidative stress are to some extent regulated by DJ1, PINK1, parkin, and HTRA2. Five genes are involved in degradation pathways, either over the lysosome or the ubiquitin-proteasomal complex. If one component in these pathways is disturbed, this might lead to dysfunction of the other components.

of Parkinson's disease is growing, the complete picture is not yet observable. How all the pathways and genes are interacting is still not completely understood. However, the discovery of new genes in conjunction with animal model studies will hopefully elucidate the pathogenesis. The standard treatment for Parkinson's disease at the moment is effective in improving the motor symptoms of the disease, but few therapies treating nonmotor features are available, and there is currently no medication at all that prevents dopaminergic neurons from dying. Identifying the proteins and understanding the pathways involved in the development of Parkinson's disease should lead to new drug targets, and might give rise to better treatment strategies.

## Disclosure

The authors report no conflicts of interest in this work.

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